# PATENT ABSTRACTS OF JAPAN

(11)Publication number : **08-133979**
(43)Date of publication of application : **28.05.1996**

(51)Int.Cl. **A61K 31/715**
**A61K 9/06**
**A61K 38/00**
**A61K 38/00**
**A61K 47/10**
**A61K 47/32**
**A61K 47/34**

(21)Application number : **07-236758**
(22)Date of filing : **14.09.1995**

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(30)Priority
Priority number : **06222031** Priority date : **16.09.1994** Priority country : **JP**

## (54) LOCALLY APPLICABLE MEDICINAL COMPOSITION

(57)Abstract:
PURPOSE: To obtain a locally applicable medicinal composition which is effective for morbid proliferation of epidermal cells and dermatoses including keratinization due to its high skin permeation and good local applicability by adding propylene glycol and a thickening agent to a composition comprising a cyclosporin compound and oleyl alcohol.
CONSTITUTION: This locally applicable medicinal composition comprises (A) a cyclosporin compound such as cyclosporin A or a macrolide compound such as 40-O-(2-hydroxy)ethyl-rapamycin or 33-epichloro-33-desoxy-ascomycin, (B) oleyl alcohol, (C) propylene glycol and (D) a thickening agent, for example, carboxyvinyl polymer or polyethylene glycol. The pharmacentical preparation form of this composition is a semisolid such as gel, paste or ointment.

LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the topical application drugs constituent which contains cyclosporin or a macrolide system compound as an active principle. It is related with the topical application which was suitable for the treatment of a dermatosis including morbid growth and/or keratinization of skin disease, especially an epidermal cell in more detail, especially a cutaneous administration constituent.
[0002]
[Description of the Prior Art] a group of the known [ cyclosporin ] of an annular undeca peptide -- it is a compound, for example, many compounds other than the compound (cyclosporin A) marketed by brand name called Sandimmun (SANDIMMUN), such as dihydrocyclosporin D and Cyclosporin G, are known (refer to JP,2-17127,A). Also in this, in the application of control of the rejection in an organ transplantation, and control of graft versus host disease, Cyclosporin A (it may only be called "cyclosporin" below) is widely used by current clinical, and is used for the serious row which cannot be dried also to Behcet's disease.
[0003] Moreover, the usefulness over various autoimmune diseases and inflammation conditions, especially the inflammation condition accompanied by the cause of a disease containing an autoimmunity element, for example, arthritis, (an example, rheumatoid arthritis, progressive spread arthritis, and hypertrophic arthritis), and a rheumatism disease is checked in in vitro one, the animal model, and a clinical trial.
[0004] Furthermore, the operation and extermination of harmful insects to malaria, coccidioidomycosis, and ******** especially the antigen student animal operation, the operation over a psilosis, and the operation over a multi-chemical resistance neoplasm are checked.
[0005] On the other hand, a macrolide system compound is large ring lactone, and the number of a ring is the generic name of the compound beyond 12 or it. A lactam system macrolide is an interesting compound which has lactam (amide) association in endocyclic in addition to lactone (ester) association, and the lactam system macrolide which the microorganism of Streptomyces groups, such as RAPAMAISHIN, ascomycin, and FK-506, produces to this, its derivative, and an analog exist in abundance. These lactams system macrolide is supposed that it has a unique pharmacological profile, and especially immunosuppression and anti-

inflammatory activity attract attention.
[0006] RAPAMAISHIN is a lactam system macrolide with an immunosuppressive action, and is produced by Streptomyces hygroscopicus. The structure of RAPAMAISHIN became clear in 1993 by Kesseler, H., etc. (Hely. Chim. Acta; 76: 117). As a derivative of RAPAMAISHIN, many classes, such as 40-O-alkylated derivatives, such as 40-O-(2-hydroxy) ethyl-rapamycin currently opened to the international public presentation/[ 94th ] No. 09010 pamphlet, are compounded. RAPAMAISHIN, its structure analogue, and a derivative are named RAPAMAISHIN generically.
[0007] Ascomycin is the lactam system macrolides of a different class, and FK-506 and ascomycin exist as a typical compound. These many have powerful immunosuppression and anti-inflammatory activity. FK-506 are Merck. The structure expression is indicated by Index and Appendix of the 11st edition (1989) as an A5 item. Ascomycin is indicated by the U.S. Pat. No. 3,244,592 specification. Many derivatives, such as halogenated derivatives, such as 33-epi-chloro-33-desoxy-ascomycin by which ascomycin and FK-506 are opened to the European Patent application public presentation No. 427680 specification, are compounded. Ascomycin, FK-506, and these structure analogue and derivatives are named ascomycin generically.
[0008]
[Problem(s) to be Solved by the Invention] However, using broadly [ until now ] because of the side effect in the injection or internal use FK-506 which are cyclosporin or a macrolide system compound for applications other than control of the rejection in an organ transplantation and the therapy of a serious autoimmune disease has been obstructed. Peter em Elias is cyclosporin and C 12-24, in order to solve this problem in above-mentioned JP,2-17127,A. The topical application constituent containing Monod, the Pori unsaturated fatty acid, or alcohol is indicated. However, it was not shown in this Peter em Elias's indication that the concrete constituent of the gestalt containing a thickener has sufficient skin permeability.
[0009]
[Means for Solving the Problem] By using propylene glycol for the constituent which consists of cyclosporin or a macrolide system compound, and oleyl alcohol as a solvent, only by finding out that high skin permeability is acquired and blending a further specific thickener, this invention person etc. finds out that the half-solid-like constituent which can hold and carry out topical application of sufficient skin permeability is obtained, and can complete this invention.
[0010] Therefore, this invention offers the topical application drugs constituent containing cyclosporin or a macrolide system compound, oleyl alcohol, propylene glycol, and a specific thickener.
[0011]
[Embodiment of the Invention] As cyclosporin, the above-mentioned cyclosporin A is desirable. Especially the amount of the cyclosporin used by this invention has 0.1 - 30 desirable % of the weight 0.01 to 40% of the weight to the total weight of a constituent, and is 0.5 - 20 % of the weight most preferably.
[0012] As a macrolide system compound, 40-O-(2-hide ROKISHI) ethyl-RAPAMAISHIN or 33-EPI-chloro-33-DESUOKISHI-ascomycin is desirable. Especially the amount of the macrolide system compound used by this invention has 0.05 - 20 desirable % of the weight 0.01 to 40%

of the weight to the total weight of a constituent, and is 0.1 - 10 % of the weight most preferably.
[0013] Especially the amount of the oleyl alcohol used by this invention has 0.5 - 30 desirable % of the weight 0.1 to 50% of the weight to the total weight of a constituent, and is 1 - 20 % of the weight most preferably.
[0014] Especially the amount of the propylene glycol used by this invention has 15 - 99.35 desirable % of the weight ten to 99.88% of the weight to the total weight of a constituent, and is 20 - 98.8 % of the weight most preferably.
[0015] The thickeners which can be used by this invention are a carboxyvinyl polymer and a polyethylene glycol (PEG).
[0016] Molecular weight about 450,000-5,000,000, especially the thing of a carboxyvinyl polymer of 1,250,000-4,000,000 are desirable. Especially an amount has 0.1 - 10 desirable % of the weight 0.01 to 25% of the weight to the total weight of a constituent, and is 0.1 - 5 % of the weight most preferably. About a carboxyvinyl polymer, what is not neutralized is easily gelable by adding neutralizers, such as triethylamine and diisopropanolamine. As for a polyethylene glycol, molecular weight about 100-100,000, especially 200-20,000 are desirable, and its thing of 1,000-20,000 is the most desirable. Especially an amount has 0.1 - 60 desirable % of the weight 0.01 to 80% of the weight to the total weight of a constituent, and is 1 - 50 % of the weight most preferably.
[0017] The formulation of the topical application drugs constituent of this invention is a half-solid, for example, gel, a paste, ointment, etc. Such formulation is suitably chosen by condition of disease, the application part, etc., and is pharmaceutical-preparation-ized by the well-known approach at this contractor.
[0018] In the constituent of this invention, a solvent, a surfactant, a preservative, a moisturizer, a coloring agent, etc. may be suitably contained other than the above-mentioned component.
[0019] Especially the constituent of this invention is applicable to the treatment of the dermatosis accompanied by morbid growth and/or keratinization of epidermis, and the therapy of the dermatitis which contains atopic dermatitis, contact dermatitis, and allergic dermatitis in the row which cannot be dried especially. Moreover, it can be used for the hair growth protection in the treatment of the psilosis which includes alopecia areata, the alopecia universalis, male pattern hair loss, other autoimmunity, or the psilosis relevant to autoimmunity associated diseases, for example, the sex psilosis which cannot be dried, for example. furthermore, it can be used for the treatment of a scales plug, a flat red moss plug, facula, and the scleroderma the skin-graft object maintenance-and heavens way right [ that ] (that being right and kind heavens way **** are included the simple **** way).
[0020] The constituent of this invention will be what contains cyclosporin or a macrolide system compound 0.5 to 10% of the weight preferably 0.1 to 20% of the weight although it changes with an indication, condition of disease, application parts, etc. on the 1st One - several times (for example, two - 5 times), 1 mg/cm2 - 20 mg/cm2 By applying to the affected part can show desirable effectiveness on clinical.
[0021]
[Example] This invention is explained in more detail using an example below.

[0022] The skin translucency test of the constituent which consists of the example cyclosporin of reference, oleyl alcohol, and a solvent (basis) was performed using 2-Chillan burr cell of drawing 1 . In the temperature of 32 degrees C, the constituent which becomes the donor phase 1 from oleyl alcohol 5% and 94% (basis) of solvents cyclosporin 1%, and 6ml of constituents which consist of cyclosporin 1% and oleyl alcohol 99% as control were put in, the amount of the cyclosporin penetrated during the receiver phase 2 filled up with the physiological saline containing 0.1% of polyoxyethylene hydrogenated castor oil 60 was measured, and the amount of transparency per unit area of the skin 3 of a hair loess rat was recorded. A result is shown in Table 1.

[0023]

[Table 1]

表 1

| 溶 剤 | 24時間目の透過量 ($\mu g/cm^2$) |
|---|---|
| コントロール（溶剤を含まず） | 0．1 |
| プロピレングリコール（PG） | 32．2（1．6） |
| 1，3－ブチレングリコール | 0．5 |
| ポリエチレングリコール400 | 0．3 |
| ポリプロピレングリコール | 0．6 |
| アジピン酸ジイソプロピル | 0 |
| 5%エタノール／PG | （1．4） |
| ミリスチン酸イソプロピル | （0） |
| 50%PG／水 | （0） |
| グリセリン | （0） |
| 50%グリセリン／水 | （0） |
| 中鎖脂肪酸トリグリセリド | （0） |

透過量は腹部皮膚を用いて測定した。（）内は背部皮膚を使用。

[0024] In the following examples and examples of a comparison, especially, as long as it is unstated, all rates are based on weight.

[0025] The cyclosporin content gel of the example 1 following presentation was manufactured.

[0026]

Cyclosporin 1% Oleyl alcohol 5% Carboxyvinyl polymer 0.2% Triethylamine 0.17% Propylene glycol The cyclosporin content ointment of the remainder example 2 following presentation was manufactured.

[0027]

Cyclosporin 1% Oleyl alcohol 5% Polyethylene glycol 4000 4.5% Propylene glycol The following examples of a comparison were performed using things other than the specific compound used with the constituent of this invention as a remainder thickener.

[0028] The cyclosporin content ointment of the example of comparison 1 following presentation was manufactured.

[0029]

Cyclosporin 1% Oleyl alcohol 5% Stearin acid 2% Propylene glycol The cyclosporin content gel of the example of remainder comparison 2 following presentation was manufactured.

[0030]

Cyclosporin 1% Oleyl alcohol 5% Light anhydrous silicic acid 5% Propylene glycol The cyclosporin content ointment of the example of remainder comparison 3 following presentation was manufactured.

[0031]

Cyclosporin 1% Oleyl alcohol 5% Paraffin 7% Myristic-acid isopropyl 11% Polysorbate 80 2% Propylene glycol The cyclosporin content ointment of the example of remainder comparison 4 following presentation was manufactured.

[0032]

Cyclosporin 1% Oleyl alcohol 5% Paraffin 7% Liquid paraffin 11% Polysorbate 80 2% Propylene glycol The cyclosporin content ointment of the example of remainder comparison 5 following presentation was manufactured.

[0033]

Cyclosporin 1% Oleyl alcohol 10% Vaseline 20% Propylene glycol The cyclosporin content gel of the example of remainder comparison 6 following presentation was manufactured.

[0034]

Cyclosporin 1% Oleyl alcohol 5% Polyoxyethylene (160) Polyoxypropylene (30) Glycol 30% Propylene glycol The skin transparency experiment was conducted by the same approach as the example of reference to the constituent of the remainder comparative-experiments examples 1 and 2 and the examples 1-6 of a comparison. A result is shown in Table 2.

[0035]

[Table 2]

表 2

| 試 料 | 24時間目の透過量 ($\mu g/cm^2$) |
|---|---|
| コントロール（増粘剤を含まず） | 32.2 (1.6) |
| 実施例 1 | 26.0 |
| 実施例 2 | 24.0 |
| 比較例 1 | 5.7 |
| 比較例 2 | 0 |
| 比較例 3 | 0 |
| 比較例 4 | 0 |
| 比較例 5 | 0 |
| 比較例 6 | 0 |

透過量は腹部皮膚を用いて測定した。() 内は背部皮膚を使用。

[0036] The constituent of examples 1 and 2 is understood that skin permeability is intentionally good compared with the constituent of the examples 1-6 of a comparison from Table 2.

[0037] The macrolide system compound content ointment of the example 3 following presentation was manufactured.

[0038]
33-EPI-chloro-33- DESUOKISHI-ascomycin 0.5% Oleyl alcohol 5% Polyethylene glycol 4000 4.5% Propylene glycol The macrolide system compound content ointment of the example of remainder comparison 7 following presentation was manufactured.
[0039]
33-EPI-chloro-33- DESUOKISHI-ascomycin 0.5% Oleyl alcohol 5% Stearin acid 2% Propylene glycol The macrolide system compound content gel of the example of remainder comparison 8 following presentation was manufactured.
[0040]
33-EPI-chloro-33- DESUOKISHI-ascomycin 0.5% Oleyl alcohol 5% Light anhydrous silicic acid 5% Propylene glycol The macrolide system compound content ointment of the example of remainder comparison 9 following presentation was manufactured.
[0041]
33-EPI-chloro-33- DESUOKISHI-ascomycin 0.5% Oleyl alcohol 5% Paraffin 7% Myristic-acid isopropyl 11% Polysorbate 80 2% Propylene glycol The macrolide system compound content gel of the example of remainder comparison 10 following presentation was manufactured.
[0042]
33-EPI-chloro-33- DESUOKISHI-ascomycin 0.5% Oleyl alcohol 5% Polyoxyethylene (160) Polyoxypropylene (30) Glycol 30% Propylene glycol The skin translucency test was performed by the same approach as the example of reference to the constituent of the remainder example 3 and the examples 7-10 of a comparison, and the amount of skin transparency of 33-EPI-chloro-33-DESUOKISHI-ascomycin was measured. A result is shown in Table 3.
[0043]
[Table 3]

表 3

| 試 料 | 24時間目の透過量 ($\mu g/cm^2$) |
|---|---|
| 実施例 3 | 27.3 |
| 比較例 7 | 0 |
| 比較例 8 | 0 |
| 比較例 9 | 0 |
| 比較例 10 | 0 |

透過量は腹部皮膚を用いて測定した。

[0044] The constituent of an example 3 is understood that skin permeability is intentionally good compared with the constituent of the examples 7-10 of a comparison from Table 3.

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CLAIMS

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[Claim(s)]
[Claim 1] The topical application drugs constituent containing cyclosporin or a macrolide system compound, oleyl alcohol, propylene glycol, and a thickener.
[Claim 2] The topical application drugs constituent according to claim 1 whose thickener is a carboxyvinyl polymer.
[Claim 3] The topical application drugs constituent according to claim 1 whose thickener is a polyethylene glycol.

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